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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09/786,317	04/27/2001	Masatoshi Hagiwara	04276.00002	8076

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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,317	HAGIWARA ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *6-8 and 10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

The Response to Restriction Requirement, filed on December 9, 2002 I, as paper No. 8, is acknowledged. Claims 1-12 are pending in the application. Claims 1-5 and 9 have been elected by Applicants without traverse, and are the subject of this Office Action. Claims 6-8, and 10-12 are withdrawn from consideration, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Detailed Office Action

1. Priority

Acknowledgment is made of Applicants' claim for priority based on an application filed in Japan on 09/02/1998.

2. Objections

2.1. Specification

A substitute specification in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) is required. The substitute specification filed must be accompanied by a statement that it contains no new matter.

The specification is objected to because the abbreviations CREB, RSGFP, (RGFP) and BSGFP (BGFP) are not expanded, see for example page 4. An abbreviation should be explained when used for the first time in the specification or claims.

2.2. Claims

Claim 4 is objected to for use of the abbreviations RSGFP and BSGFP that are not expanded.

2.3. Drawings

This application has been filed with informal drawings, which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

3. Rejections

3.1. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 1-5 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "a protein comprising at least the phosphorylation region" in line 4. There is insufficient antecedent basis for this limitation in the claim. The claim is unclear in reciting the phrase “a protein comprising at least the

phosphorylation region" because the phrase relates to part a) of the claim, but part a) does not recite a protein comprising at least the phosphorylation region.

Claims 2-5 and 9 are included in this rejection, because they are dependent upon claim 1 and do not correct its deficiency.

2.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Lack of written description

Claim 1-5 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a monitor protein comprising a variable property region or to a use of such monitor protein. The claims are generic, because the term "variable property region" describes a variable genus of chemical molecules (polypeptides, proteins and others) whose properties can be changed by

phosphorylation of attached phosphorylation region of the monitor protein. The only representative species of the claimed genus are two green fluorescent proteins from *Aequorea victoria* fused to the CREB fragment of SEQ ID NO:1. Applicants failed to set forth any identifying characteristic of the other representatives of the genus.

In addition, it is not certain that any fusion of RSGFP and BSGFP protein from *Aequorea victoria* to any phosphorylation region will produce a monitor protein as claimed in claim 4. The claim is directed to a genus of fusion proteins, however, the only fusion protein species disclosed by Applicants consists of SEQ ID NO:1 and the RSBFP and BSGFP. The disclosure is silent as to what is an identifying characteristics of the phosphorylation region that is critical for changes in fluorescence of the fusion protein in result of phosphorylation of its phosphorylation region.

In conclusion, Applicants failed to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize they were in possession of the claimed invention.

2.2.2. Scope of enablement

Claims 1-5 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the variable property region consisting of two green fluorescence proteins form *Aequorea victoria* does not reasonably provide enablement for any other chemical molecule that shows a property change caused by phosphorylation of the phosphorylatioh region of the monitor protein; see the above rejection for lack of written description. The scope of the claims covers any fusion

protein that shows a property change caused by phosphorylation of the phosphorylation region.

The claims are broader in scope than the enablement set forth in the specification. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any protein that shows a property change caused by phosphorylation of a phosphorylation region. The genus of molecules encompasses any protein including a phosphorylation region said protein can be subsequently tested for change of a property caused by phosphorylation of the phosphorylation region. Although synthesis of hybrid molecules in well known in the art and skills of artisan high, no one is able to bind any chemical molecule to the phosphorylation region of the monitor protein and test which physical /chemical properties of said molecule has changed in result of phosphorylation. Applicants provide only the guidance regarding the use of two green proteins from *Aequorea victoria* and SEQ ID NO: 1 as components of the fusion monitor protein. It is unpredictable what

phosphorylation region and "what variable properties" regions can be fused such that there will be a change in the properties of the variable property region after phosphorylation. In addition, the disclosure does not teach how to select phosphorylation region and variable property region, neither a guidance is provided as to the way both components of the fusion protein will be fused to form the monitor protein. Without further guidance on the part of Applicants as to the nature and structure of the claimed variable property region and phosphorylation region experimentation left to those in the art is improperly extensive and undue.

3.3. 35 USC section 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 1, 2, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by the US Patent No. 5,925,558, with effective filing date July 16, 1996, issued on July 20, 1999, enclosed in Information Disclosure Statement.

Claims 1 and 9 are directed to a monitor protein and its use wherein the monitor protein consists of a phosphorylation region comprising (a) amino acid residue or amino acid sequence to be phosphorylated and (b) a variable property region showing a property change attributed to a conformational change of phosphorylation region caused by its phosphorylation. Claim 2 is directed to said monitor protein wherein the variable property region is a protein that emits fluorescence.

The patent discloses fluorescent proteins that are modified to incorporate a phosphorylation site recognized by a protein kinase. The proteins not only can become phosphorylated by the protein kinase, but they can also exhibit different fluorescent characteristics in their un-phosphorylated and phosphorylated forms when irradiated with light having a wavelength within their excitation spectrum; the patent, column 2, line 63, "Summary of the Invention". The patent also discloses a method for determining whether a sample has a phospohrylation ability; see column 3, line 5.

Thus, the patent discloses the inventions claimed in claim 1, 2 and 9 of the instant application, because the patent discloses a protein consisting of (a) amino acid sequence to be phosphorylated and (b) a variable property region showing a property

change attributed to a conformational change of phosphorylation region caused by its phosphorylation, wherein said variable property region is a protein that emits fluorescence, and because the patent discloses the use of said protein for testing the phosphorylation ability of the other proteins.

3.4. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over the US Patent 5,925,558, with effective filing date July 16, 1996, issued on July 20, 1999, and further in view of the publication by Hagiwara M. et al. (Coupling of Hormonal Stimulation and Transcription via he Cyclic AMP-Responsive Factor CREB Is Rate Limiting by Nuclear Entry of Protein Kinase A, Molecular and cellular Biology, 1993, 13, 4852-4859, included in the Information Disclosure Statement).

The claim is directed to a monitor protein consisting of (a) a phosphorylation region comprising the amino acid sequence of SEQ ID NO: 1 and (b) a variable property region showing a property change attributed to a conformational change of SEQ ID NO: 1 caused by its phosphorylation, wherein a variable property region is protein that emits fluorescence.

The patent teaches proteins having phosphorylation regions that are different substrates for phosphorylation by kinase A, see claims 1, 2, 3 of the patent. The proteins contain also fluorescent proteins from *Aequorea*. The patent does not teach the protein containing the substrate for kinase A wherein said substrate is set forth by SEQ ID NO: 1; a fragment of the transcription factor CREB.

Hagiwara et al. teach that kinase A phosphorylates CREB transcription factor at its 133 residue, which is serine; see, for example, the second line of the abstract. Hagiwara et al. do not teach a fusion protein of the fragment of CREB containing residue 133 (SEQ ID NO: 1) and a fluorescent protein.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the protein disclosed in the patent and modify it so that it contains as a phosphorylation region of yet another substrate of kinase A; for example a fragment comprising the 133 Ser of transcription factor CREB as does SEQ ID NO: 1.

The expectation of success was very high because the patent shows that many substrates for kinase A can be used for construction of the monitor protein.

The motivation was also provided by the patent because the patent has presented evidence that a hybrid protein containing the substrate for kinase A and

fluorescent protein from *Aequorea* can be use as a monitor protein for measuring phosphorylation ability of a test protein.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claim 4 might seem to be obvious in the light of the publication by Romoser V. et al (Detection in living cells of Ca^{2+}-dependent changes in the fluorescence emission of an indicator composed of two green fluorescent protein variants linked by a calmodulin-binding sequence, J. Biol. Chem. 1997, 272, 13270-13274) or Miyawaki A. et al, Fluorescent indicators from Ca^{2+} based on green fluorescent proteins and calmodulin, Nature, 1997, 388, 882-887).

The Romoser et al.'s publication discloses a fusion proteins comprising calmodulin with two green fluorescent proteins bound to its ends, wherein the fusion protein exhibits change of the fluorescent properties (fluorescence resonance energy transfer, FRET) upon changes in conformation of calmodulin induced by attachment of Ca^{2+}. Although the inventor used the same plasmid as Romoser et al. for production of their "monitor" protein, wherein nucleotide sequence encoding calmodulin was replaced by the nucleotide sequence encoding SEQ ID NO: 1 but both fluorescent proteins were the same, it was not obvious that phosphorylation of SEQ ID NO: 1 would brought conformational changes of SEQ ID NO: 1 resulting in FRET between both fluorescent proteins.

4. Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

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